REMARKS

I. Status Summary

Claims 1, 3-12, 14-18 and 20-46 are pending in the subject application. Claims 17-25, 29-41 and 43-35 have been withdrawn from consideration pursuant to the February 15, 2005 Restriction Requirement. Claims 1, 3-11, 16, 26-28, 42, and 46 have been examined by the U.S. Patent and Trademark Office (hereinafter "the Patent Office"). Claims 1, 3-11, 16, 26-28, 42, and 46 presently stand rejected. In light of remarks made by applicants in response to the Official Action dated August 10, 2005, claim 15 is also now included in the consideration and also stands rejected.

Claims 1, 3-11, 15, 16, 26-28, 42 and 46 are rejected under 35 U.S.C. 112, first paragraph upon the Patent Office contention that the specification, while being enabling for mutants of bovine gamma-crystallin of SEQ ID NO:22 obtained by mutations at positions identified in claim 12, does not reasonably provide enablement for mutants of other crystallins, much less for other proteins with mutations at beta sheet structure as claimed.

Claims 12 and 15 are objected to as being dependent upon a rejected base claim.

Claims 3 and 4 have been canceled without prejudice.

Claim 1 has been amended herein. Specifically, the phrase "located in at least two beta strands of at least one beta sheet" has been removed and the residues are more particularly described. Claim 1 now recites that the protein has an "antibody-like binding activity towards a binding partner", and that the mutagenization occurs "in two, three, or four beta-strands of at least one beta-sheet of said protein with beta-sheet structure; said beta-sheet, said beta-strands and said amino acids" being "located on a surface of said protein". The amendments to claim 1 are supported throughout the subject U.S. patent application as filed, including by claims 3 and 4, as well as in the specification on page 2, lines 9-11, and page 7, lines 9-16 and 24-31.

Claims 42 and 46 have been amended in a manner similar to claim 1. Specifically, the phrase "located in at least two beta strands of at least one beta

sheet", which was objected to by the Patent Office, has been removed and the residues more particularly described. The protein of claims 42 and 46 as amended must have an "antibody-like binding activity towards a binding partner", and the mutagenization must occur "in two, three or four beta-strands of at least one beta-sheet of said protein with beta-sheet structure; said beta-sheet, said beta-strands and said amino acids" being "located on a surface of said protein". Claims 42 and 46 as amended are supported in the application as filed by claims 3 and 4; as well as on page 2, lines 9-11, and on page 7, lines 9-16 and 24-31.

Claims 7, 42-44, and 46 have been amended to correct certain typographical errors. Particularly, all recitations of "crystalline" have been amended to "crystallin", and the recitation of "spheruline" has been amended to "spherulin". Additionally, recitations of "gamma crystallin" have been amended to "gamma-crystallin". These amendments are for the purpose of correcting these typographical errors only, and are not to be interpreted as a surrender of any subject matter encompassed by the claims prior to the amendments.

No new matter has been added.

Reconsideration of the subject U.S. patent application based on the amendments and arguments set forth herein is respectfully requested.

II. Response to the 35 U.S.C. §112, First Paragraph, Enablement Rejection

Claims 1, 3-11, 15, 16, 26-28, 42 and 46 have been rejected under 35 U.S.C. 112, first paragraph upon the Patent Office contention that the specification, while being enabling for mutants of bovine gamma-crystallin of SEQ ID NO:22 obtained by mutations at positions identified in claim 12, does not reasonably provide enablement for mutants of other crystallins, much less for other proteins with mutations at beta sheet structure as claimed.

Initially, without acquiescing to the contentions made by the Patent Office, claims 1, 42, and 46 have been amended. Specifically, the phrase "located in at least two beta strands of at least one beta sheet" has been removed and the residues more particularly described. Further claims 1, 42, and 46 now recite that the protein has an "antibody-like binding activity towards a binding partner", and the

mutagenization occurs "in two, three or four beta-strands of at least one beta-sheet of said protein with beta-sheet structure; said beta-sheet, said beta-strands and said amino acids" being "located on a surface of said protein". Claims 1, 42, and 46 as amended are supported in the application as filed by claims 3 and 4; as well as in the specification on page 2, lines 9-11, and on page 7, lines 9-16 and 24-31.

Continuing with the instant rejection, the Patent Office has rejected claims 1, 3-11, 15, 16, 26-28, 42 and 46 under 35 U.S.C. §112, first paragraph, upon the contention that "the specification, while being enabling for mutants of bovine gamma-crystallin of SEQ ID No. 22 obtained by mutations at positions identified in claim 12, does not reasonably provide enablement for mutants of other crystallins, much less for other proteins with mutations at beta sheet structure as claimed". Official Action at pages 2-3. Applicants respectfully traverse this rejection and submit the following comments.

As a matter of Patent Office practice, the burden rests upon the Patent Office to establish a prima facie case of a failure to comply with 35 U.S.C. § 112, first paragraph, with respect to the invention described and claimed in applicants' presumptively enabling patent application. See In re Marzocchi, 58 C.C.P.A. 1069, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A. 1971).

It is contended by the Patent Office that the present U.S. patent application does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with the claims. However, no specific scientific or other factual basis in support of this contention has been presented in the Official Action. The Patent Office has offered only one citation of a journal article (Guo), which is not believed to be applicable to the presently claimed subject matter for the reasons set forth herein below. The Patent Office has not made reference to any other scientific literature or other information which would serve to support this contention, as is required under In re Marzocci. Rather, a series of conclusory statements have been made, contending that the U.S. patent application is enabling only for mutants of bovine gamma-crystallin of SEQ ID NO:22 obtained by mutations at positions identified in claim 12.

Applicants therefore respectfully submit that a prima facie case of a lack of enablement under 35 U.S.C. §112, first paragraph, has not been made.

Indeed, 35 U.S.C. §112, first paragraph, requires no more than a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of the claims, and this requirement has clearly been met. Claims 3 and 4 have been canceled, and thus the rejection is believed to be moot as to these claims. Accordingly, claims 1, 5-11, 15, 16, 26-28, 42 and 46 are in compliance with 35 U.S.C. §112, first paragraph. Withdrawal of this rejection of these claims is respectfully requested.

However, assuming arguendo that a prima facie case of a failure to comply with 35 U.S.C. §112, first paragraph, has been made, applicants respectfully submit the following. The Patent Office's primary contention in support of the rejection under 35 U.S.C. §112, first paragraph, appears to be that a large amount of experimentation would be required to identify other mutants. Official Action, page 3, lines 1-3 and page 4, lines 9-12. It also appears that it is the Patent Office's position that 35 U.S.C. §112, first paragraph, requires the presentation of working examples. Official Action, page 4, lines 9-12.

Applicants respectfully submit that an inappropriate standard for measuring enablement under 35 U.S.C. §112, first paragraph has been adopted. The appropriate standard is that the claimed subject matter must be enabled so that a person skilled in the art can make and use the subject matter from the disclosures of the U.S. patent application, coupled with information known in the art, without "undue experimentation". In re Wands, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988).

First, it is contended in the Official Action that "with the insufficient guidance and working examples and in view of unpredictability and the state of art one skilled in the art could not make and/or use the invention with the claimed breadth without an undue amount of experimentation". Official Action page 4, lines 9-12. However, while it might require considerable experimentation to arrive at and/or characterize additional mutagenized polypeptides that have acquired the recited antibody-like binding specificities, the quantity of experimentation to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation"

is required to make and use the invention. "An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." In re Colianni, 195 U.S.P.Q. 150, 153 (C.C.P.A. 1977). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the U.S. patent application in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed." In re Wands, 8 U.S.P.Q.2d at 1404 (citing In re Angstadt, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976)). Time and expense are merely factors in this consideration and are not the controlling factors. U.S. v. Telectonics, Inc., 8 U.S.P.Q.2d 1217, 1223 (Fed. Cir. 1988), cert. denied, 490 U.S. 1046 (1989). It is further noted the level of skill in this art is high. As noted in the In re Wands decision, this factor must also be considered in evaluating compliance with 35 U.S.C. §112, first paragraph.

While the presence or absence of working examples is one consideration in the overall evaluation of enablement, working examples are not required under 35 U.S.C. §112, first paragraph, to comply with the enablement standard presented therein. Indeed, the M.P.E.P. states that the U.S. patent application need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation. M.P.E.P. §2164.02. The M.P.E.P. also states that a lack of working examples or lack of evidence that the claimed invention works as described should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement. Id. (emphasis added).

Turning now to the guidance provided in the disclosure of the present U.S. patent application as filed, disclosed are proteins selected from the group consisting of a crystallin, a spherulin, a heat-shock protein, a cold-shock protein, a beta-helix protein and a fibronectin. This group of proteins is highly related to one another, as would be recognized by one of skill in the art. Claim 1 is directed to this group of related proteins; and claim 46 is also directed to this group of related proteins. Claim 42 specifically recites a gamma-crystallin polypeptide. Due to this close relationship in the beta-structures and other structural motifs, a person of ordinary

skill in the art could apply the techniques disclosed in the present disclosure with respect to gamma-crystallin to the other proteins recited in claims 1, 42, and 46 without any undue experimentation.

It is respectfully noted that unlike the Patent Office's apparent assertion, the presently disclosed subject matter does not rely on any ability of the skilled artisan to predict the functional outcomes of specific mutations. Rather, what the presently disclosed subject matter provides is a protein having a desired functionality (binding specificity or activity), wherein it is not necessary to know beforehand which mutation(s) will result in the desired function. Indeed, as the nature of any screening assay is to start with a large number of samples and from that large group select the few samples that have the characteristics of interest.

In some embodiments, the proteins to be mutated (*e.g.*, the crystallins) are structural proteins which do not possess any binding activity at all. In accordance with the presently disclosed subject matter, these proteins are mutagenized in accordance with the elements recited in claims 1, 42, and 46 in order to acquire an antibody-like binding activity with respect to a selected binding partner. In order to express the new property of the mutagenized protein, which is defined in relationship with a second element (the binding partner), claims 1, 42, and 46 have been amended to recite a protein with an antibody-like binding activity towards a binding partner. Thus, claims 1, 42, and 46 recite proteins that have been modified in order to obtain a binding activity to a binding partner wherein the binding activity is similar to that of an antibody. The binding of an antibody to an antigen is well known in the art, and in the presently claimed subject matter proteins selected as described in claims 1, 42, and 46 are mutagenized in such a way that the resulting proteins behave with respect to their binding activity like an antibody to an antigen binding partner. Related disclosure can be found in the subject U.S. patent application as filed, for instance, on page 2, second paragraph.

The Examiner notes on page 3 of the Official Action that the specification teaches a protein that was selected from 26 billion protein sequences, suggesting that such searches would require undue experimentation on the part of one skilled in the art. However, it is routine in the art to conduct large screening assays in which

thousands or even billions of clones are screened in as little as a matter of days. The Examiner is reminded (for example, please see page 17, lines 21-24) that although as many as 26 billion protein sequences can be obtained by the given mutational method, the next steps in processing such mutants are efficient and routine in the art, and can include methods such as phage display (described on page 11, No. 1 of the specification) and non-phage display methods (described on page 11, No. 2 of the specification). Such methods of screening mutants are efficient, fast, and well-known in the art, and serve to quickly pare down the number of mutants by allowing selection of only those mutants containing the desired properties or characteristics. For example, the analysis can be done towards a potential binding partner, and only those mutagenized proteins are selected which provide the desired antibody-like binding activity towards the antigen selected as binding partner. Thus, as noted above, "an extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." In re Colianni, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977).

Certainly, the instant specification provides sufficient guidance for one of skill in the art to practice the presently disclosed subject matter using techniques that are either described in the specification or are well known in the art, such as the methods on page 11 of the specification (*see* above). Thus, the guidance supplied in the present U.S. patent application would enable one of skill in the art to practice the instantly claimed subject matter without undue experimentation.

The Patent Office further states that there is "a lack of guidance (except for gamma-crystalline of SEQ ID No. 22) for what elements of structure can be mutagenized to obtain mutants with the claimed functional activity." Official Action, page 4, lines 17-19. Applicants respectfully disagree and submit the following comments.

The Patent Office also contends that the "breadth of the claims encompasses any protein comprising a beta sheet and mutated at any residue located in at least two beta strands of at least one beta sheet". The claims as amended recite that the mutations are located in two, three, or four beta-strands of at least one beta-sheet of one of the proteins of present claims 1, 42, and 46, which all have a beta-sheet

structure. Additionally, it is recited that the beta-sheet, the beta-strands, and the amino acids located therein are also located on the surface of the protein, thus specifying in further detail the location of the mutations. Thus, the amino acids to select in order to provide the claimed protein are believed to be clearly recited.

Further, the number of amino acids in one beta strand is small. Indeed, as would apparent to one of ordinary skill in the art upon a review of the present disclosure, the number of amino acids in any given beta-strand is generally 7-8, and approximately half of these amino acids are typically surface-exposed. Due to this limited number of amino acids in each beta-strand and the number of beta-strands as recited in claims 1, 42, and 46, there is believed to be a manageable number of amino acid that can be mutagenized. As mutagenization can be performed in a random manner, specific guidance for the other proteins with respect to which particular amino acids to be selected for mutagenization is not necessary. As described herein above, in a screening method using the interaction between the randomly mutated protein on the one side and the selected antigen binding partner on the other side, those mutated proteins are found which possess the properties selected by the researcher.

On page 3 of the Official Action, the Patent Office asserts in a footnote that the specification does not confirm that the selected residues of gamma-crystallin are indeed located in at least two beta-strands of at least one beta-sheet as recited in the claims. Enclosed please find a true and accurate copy of a Declaration Pursuant to 37 C.F.R. §1.132 providing additional data confirming that the example of the provided in the instant U.S. patent application is in accordance with claims 1 and 46.

Summarily, applicants respectfully submit that the U.S. patent application of the present U.S. patent application provides adequate guidance and instruction such that one having ordinary skill in the art can make and use the present invention as claimed in pending claims 1, 5-11, 15, 16, 26-28, 42 and 46. Indeed, applicants respectfully submit that 35 U.S.C. §112, first paragraph, requires no more than a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate in the scope of the claims, and this requirement has been clearly met. Accordingly, claims 1, 5-11, 15, 16, 26-28, 42 and 46 are believed to be in

compliance with 35 U.S.C. §112, first paragraph, and allowance of claims 1, 5-11, 15, 16, 26-28, 42 and 46 is respectfully requested.

CONCLUSION

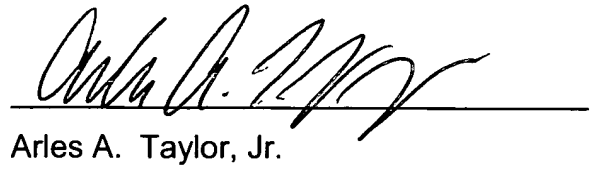
In light of the above amendments and remarks, it is respectfully submitted that claims 1, 5-12, 14-16, 26-28, 42, and 46 of the present U.S. patent application are now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any deficiency in payment or credit any overpayment of fees associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,
JENKINS, WILSON, TAYLOR, & HUNT, P.A.

Date: September 12, 2006 By: 

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